WHAT IS CLAIMED IS:

1. A method for mitigating post-implantation calcification of a bioprosthetic material, said method comprising the steps of:

(a) heating a glutaraldehyde solution to a first temperature for a first period of time;

(b) adjusting the temperature of the glutaraldehyde solution to a second temperature; and,

(c) after the temperature of the glutaraldehyde solution has been adjusted to the second temperature, contacting a quantity of biological tissue that contains connective tissue protein with the glutaraldehyde solution for a second period of time.

2. A method according to Claim 1, wherein the first temperature is maintained for a period of time until a predetermined end point is reached, said predetermined end point being indicated by at least one indicator selected from:

a decrease of about 25 % or more in the free aldehyde content of the solution;

a fall in the pH of the solution from about 7.4 to about 6.0;

a fall in the pH of the solution by about 20%; and,

a change in the color of the solution to yellow or brown.

3. A method according to Claim 2 wherein the first temperature is about 20-90°C.

4. A method according to Claim 2 wherein the first temperature is about 60-80°C.

5. A method according to Claim 2 wherein the first temperature is about 70 ± 5°C.

6. A method according to Claim 2 wherein the second temperature is less than the first temperature.

7. A method according to Claim 6 wherein the second temperature is about 30-70°C.

8. A method according to Claim 6 wherein the second temperature is about 40-60°C

9. A method according to Claim 6 wherein the second temperature is about 50 ± °C.

10. A method according to Claim 1 wherein the first temperature is no lower than about 70°C and the second temperature is no higher than about 60°C.

11. A method according to Claim 10 wherein the first period of time is one hour to six months.

12. A method according to Claim 10 wherein the second period of time is shorter than the first period of time.

13. A method according to Claim 1 wherein the tissue is at least partially fixed prior to the performance of Step (c).

14. A method according to Claim 1 wherein the tissue is fixed after the performance of Step (c).

15. A method according to Claim 1 wherein the tissue is fixed concurrently with the performance of Step (c).

16. A method according to Claim 15 wherein the tissue is fixed concurrently with the performance of Step (c) by immersing the tissue in a solution that contains the glutaraldehyde that was heat-treated in Step (a) as well as a fixative agent.

17. A method according to Claim 16 wherein the fixative agent is non-heat-treated glutaraldehyde.

18. A method according to Claim 17 wherein the fixative agent is selected from the group of fixative agents consisting of:

(a) aldehydes;

(b) polyglycidyl ethers;

(c) heterologous multifunctional crosslinkers; and

(d) combinations of aldehydes, polyglycidyl eithers and heterologous multifunctional crosslinkers.

19. A method according to Claim 1 wherein the tissue is fixed in the glutaraldehyde solution in Step (c) while the solution is moving relative to the tissue.

20. A method according to Claim 1 wherein the method further comprises:

preparing a solution of 0.1-25% by weight glutaraldehyde;

heating the glutaraldehyde solution to about 20-90°C in Step (a);

adjusting the second temperature to no greater than about 60°C; and

thereafter immersing the tissue in the glutaraldehyde solution in Step (c) while maintaining the temperature of the solution in the range of about 40°C to 60°C for about 1 day to two months.

21. A method according to Claim 20 further comprising the step of adding any desired non-biological components to the tissue and fabricating a bioprosthesis.

22. A method according to Claim 20 further comprising the step of subjecting the tissue to a bioburden reduction process.

23. A method according to Claim 22 wherein the step of subjecting the tissue to a bioburden reduction process comprises contacting the tissue with a bioburden reduction solution containing a surfactant, an aldehyde and an alcohol.

24. A method according to Claim 23 wherein the bioburden reduction solution comprises:

Formaldehyde.....2-10 % by weight;

Ethanol.....10-45% by weight; and,

Tween 80.....0.1-10% by weight.

25. A method according to Claim 20 further comprising the steps of:

adding any desired non-biological components to the tissue and fabricating a bioprosthesis; and,

sterilizing the bioprosthesis.

26. A method according to Claim 1 further comprising the steps of:

removing the tissue from the heat-treated glutaraldehyde solution;

subjecting the tissue to a first bioburden reduction process;

adding any desired non-biological components to the tissue and fabricating a bioprosthesis;

subjecting the tissue to a second bioburden reduction process; and,

sterilizing the bioprosthesis.

27. A method according to Claim 1 further comprising the step of sterilizing the tissue.

28. A method according to Claim 27 wherein the sterilization of the tissue comprises:

contacting the tissue with a terminal sterilization solution and heating said terminal sterilization solution to a temperature between about 20 to 50°C for a period of time sufficient to ensure the sterility of the bioprosthesis until the time of implantation.

29. A method according to Claim 28 wherein the sterilization is carried out in a sealed container and further comprises allowing the tissue to remain within said sealed container until the time of implantation.

30. A method according to claim 28 wherein the sterilization is carried out in a moving glutaraldehyde solution.

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31. A method according to Claim 28 wherein said terminal sterilization solution comprises an aqueous solution of 0.2-1.0% by weight glutaraldehyde buffered to a pH of approximately 7.4.

32. A method according to Claim 28 wherein the terminal sterilization solution comprises osmotically balanced salt solution in combination with at least one chemical sterilant.

33. A method according to Claim 28 wherein the terminal sterilization solution comprises at least one component selected from i) a denaturant, ii) a surfactant, and iii) a crosslinking agent.

34. A method according to Claim 28 wherein the sterilization solution comprises the previously heated and cooled glutaraldehyde solution prepared in Steps (a) and (b) of Claim 1 and wherein the tissue treatment of Step (c) is carried out concurrently with the sterilization step of Claim 27.

35. A method according to Claim 1 wherein the tissue is sterilized after Step (c) by an in-container terminal sterilization process comprising the steps of:

providing a container which contains a quantity of a terminal sterilant solution comprising 0.2-1.0 % by weight glutaraldehyde buffered to a pH of approximately 7.4;

immersing the tissue in said terminal sterilant solution within said container;

sealing said container;

heating said container, and the terminal sterilant solution and bioprosthesis contained therein, to a temperature of about 37-50°C for a period of about six hours to six days;

cooling said container, and the terminal sterilant solution and bioprosthesis contained therein, to room temperature; and,

allowing said container to remain sealed until it is desired to implant the bioprosthesis in a mammalian patient.

36. A bioprosthesis comprising tissue that has been subjected to a calcification mitigation treatment comprising the steps of :

(a) heating a glutaraldehyde solution to a first temperature for a first period of time;

(b) adjusting the temperature of the glutaraldehyde solution to a second temperature; and,

(c) after the temperature of the glutaraldehyde solution has been adjusted to the second temperature, contacting the glutaraldehyde solution with a quantity of biological tissue that contains connective tissue protein for a second period of time.

37. A bioprosthesis according to Claim 36 wherein the bioprosthesis comprises a tissue selected from the group of tissues consisting of:

cardiac valves;

blood vessels;

skin;

dura mater;

pericardium;

ligaments;

tendons;

small intestinal submucosa; and,

combinations of cardiac valves, blood vessels, skin, dura mater, pericardium, ligaments, tendons, and small intestinal submucosa.

38. A bioprosthesis according to Claim 36 wherein the glutaraldehyde contacted with the biological tissue in step (c) is prepared by heating glutaraldehyde, in the absence of the biological tissue, until a predetermined end point is reached said predetermined end point being indicated by at least one indicator selected from:

a decrease of about 25 % or more in the free aldehyde content of the solution;

a fall in the pH of the solution from about 7.4 to about 6.0;

a fall in the pH of the solution by about 20%; and,

a change in the color of the solution to yellow or brown.

39. A bioprosthesis according to Claim 36 wherein the first temperature is about 20-90°C.

40. A bioprosthesis according to Claim 36 wherein the first temperature is about 60-80°C.

41. A bioprosthesis according to Claim 36 wherein the first temperature is about 70 ± 5°C.

42. A bioprosthesis according to Claim 36 wherein the second temperature is less than the first temperature.

43. A bioprosthesis according to Claim 42 wherein the second temperature is about 30 to 70°C.

44. A bioprosthesis according to Claim 42 wherein the second temperature is about 40 to 60°C

45. A bioprosthesis according to Claim 42 wherein the second temperature is about 50 ± 5°C.

46. A bioprosthesis according to Claim 36 wherein the first temperature is no lower than about 70°C and the second temperature is no higher than about 60°C.

47. A bioprosthesis according to Claim 39 wherein the first period of time is one hour to six months.

48. A bioprosthesis according to Claim 46 wherein the second period of time is shorter than the first period of time.

49. A bioprosthesis according to Claim 48 wherein the first temperature is about 70-80°C, the first period of time is about one day to two months and the second period of time is about 5 to 10 days.

50. A bioprosthesis according to Claim 36 wherein the second period of time is less than the first period of time.

51. A bioprosthesis according to Claim 36 wherein the tissue is at least partially fixed prior to the performance of Step (c).

52. A bioprosthesis according to Claim 36 wherein the tissue is fixed after the performance of Step (c).

53. A bioprosthesis according to Claim 36 wherein the tissue is fixed concurrently with the performance of Step (c).

54. A bioprosthesis according to Claim 53 wherein the tissue is fixed concurrently with the performance of Step (c) by immersing the tissue in a solution that contains the glutaraldehyde that was heat-treated in Step (a) as well as a fixative agent.

55. A bioprosthesis according to Claim 54 wherein the fixative agent is non-heat-treated glutaraldehyde.

56. A bioprosthesis according to Claim 55 wherein the fixative agent is selected from the group of fixative agents consisting of:

aldehydes;

polyglycidyl eithers;

heterologous multifunctional crosslinkers; and

combinations of aldehydes, polyglycidyl eithers, and heterologous multifunctional crosslinkers.

57. A bioprosthesis according to Claim 36 wherein the method by which the bioprosthesis is treated further comprises:

preparing a solution of 0.1-25% by weight glutaraldehyde;

heating the glutaraldehyde solution to 20-90°C in Step (a);

adjusting the temperature of the glutaraldehyde solution to a temperature no greater than about 60°C and buffering the pH of the solution at that adjusted temperature to approximately 7.4; and

thereafter immersing the tissue in the glutaraldehyde solution in Step (c) while maintaining the temperature of the solution in the range of about 40°C to 60°C for about 1-15 days.

58. A bioprosthesis according to Claim 57 wherein the method by which the bioprosthesis is treated further comprises the step of adding any desired non-biological components to the tissue and fabricating a bioprosthesis.

59. A bioprosthesis according to Claim 57 wherein the method by which the bioprosthesis is treated further comprises the step of subjecting the tissue to a bioburden reduction process.

60. A bioprosthesis according to Claim 59 wherein the step of subjecting the tissue to a bioburden reduction process comprises contacting the tissue with a bioburden reduction solution containing a surfactant, an aldehyde and an alcohol.

61. A bioprosthesis according to Claim 60 wherein the bioburden reduction solution comprises:

Formaldehyde.....2-10 % by weight;

Ethanol.....10-45% by weight; and,

Tween 80.....0.1-10% by weight.

62. A bioprosthesis according to Claim 36 wherein the method by which the bioprosthesis is treated further comprises the steps of:

adding any desired non-biological components to the tissue and fabricating a bioprosthesis; and,

sterilizing the bioprosthesis.

63. A bioprosthesis according to Claim 36 wherein the method by which the bioprosthesis is treated further comprises the steps of:

removing the tissue from the heat-treated glutaraldehyde solution;

subjecting the tissue to a first bioburden reduction process;

adding any desired non-biological components to the tissue and fabricating a bioprosthesis;

subjecting the tissue to a second bioburden reduction process; and,

sterilizing the bioprosthesis.

64. A bioprosthesis according to Claim 36 wherein the method by which the bioprosthesis is treated further comprises the step of sterilizing the tissue.

65. A bioprosthesis according to Claim 64 wherein the sterilization of the tissue comprises contacting the tissue with a terminal sterilization solution and heating said terminal sterilization solution to a temperature between about 37 to 50°C for a period of time sufficient to ensure the sterility of the bioprosthesis until the time of implantation.

66. A bioprosthesis according to Claim 65 wherein the sterilization is carried out in a sealed container and further comprises allowing the tissue to remain within said sealed container until the time of implantation.

67. A bioprosthesis according to Claim 65 wherein said terminal sterilization solution comprises an aqueous solution of 0.2-1.0% by weight glutaraldehyde buffered to a pH of approximately 7.4.

68. A bioprosthesis according to Claim 65 wherein the terminal sterilization solution comprises osmotically balanced salt solution in combination with at least one chemical sterilant.

69. A bioprosthesis according to Claim 65 wherein the terminal sterilization solution comprises at least one component selected from i) a denaturant, ii) a surfactant, and iii) a crosslinking agent.

70. A bioprosthesis according to Claim 36 wherein the bioprosthesis is sterilized after Step (c) by an in-container terminal sterilization process comprising the steps of:

providing a container which contains a quantity of a terminal sterilant solution comprising 0.2-1.0 % by weight glutaraldehyde buffered to a pH of approximately 7.4;

immersing the bioprosthesis in said terminal sterilant solution within said container;

sealing said container;

heating said container, and the terminal sterilant solution and bioprosthesis contained therein, to a temperature of about 37-60°C for a period of about six hours to six days;

cooling said container, and the terminal sterilant solution and bioprosthesis contained therein, to room temperature; and,

allowing said container to remain sealed until it is desired to implant the bioprosthesis in a mammalian patient.

71. A bioprosthesis according to Claim 65 wherein the terminal sterilization solution is the glutaraldehyde solution that was heat-treated and cooled in Steps (a) and (b) of Claim 1 and wherein the treatment of the tissue of Step (c) is carried out concurrently with the terminal sterilization of the bioprosthesis.

72. A method for mitigating post-implantation calcification of a bioprosthetic material, said method comprising the steps of:

(a) adjusting the pH of a solution selected from the group consisting of a glutaraldehyde solution and a physiologic solution, to a pH in the range of about 5.0 to 7.0;

(b) contacting a quantity of biological tissue that contains connective tissue protein with the solution; and

(c) heating the solution and the tissue to a temperature in the range of about 30 to 70 ° C for a period of time.

73. A method according to Claim 72, wherein the pH is adjusted to about 6.0.

74. A method according to Claim 72, wherein the temperature is in the range of about 40 to 60 ° C.

75. A method according to Claim 72, wherein the temperature is about 50° C ± 5° C.

76. A method according to Claim 72, wherein the period of time is between about one hour and six months.

77. A method according to Claim 72, wherein the period of time is between about one day and two months.

78. A method for mitigating post-implantation calcification of a bioprosthetic material, said method comprising the steps of:

(a) heating a solution selected from the group consisting of a solution comprising a fixative agent, a solution comprising a surfactant, and a physiologic solution, to a first temperature in the range of about 20 to 90° C for a first period of time;

(b) adjusting the solution from step (a) to a second temperature in the range of about 30 to 70 ° C; and

(c) then treating the bioprosthetic material with the solution from step (b) for a second period of time.

79. A method according to Claim 78, wherein the first temperature is in the range of about 37 to 60 ° C.

80. A method according to Claim 78, wherein the first temperature is about 45° C ± 5° C.

81. A method according to Claim 78, wherein the first period of time is between about one hour and six months.

82. A method according to Claim 78, wherein the first period of time is between about one day and two months.

83. A method according to Claim 78, wherein the second temperature is in the range of about 40 to 60 ° C.

84. A method according to Claim 78, wherein the second temperature is about 50° C ± 5° C.

85. A method according to Claim 78, wherein the second period of time is between about one hour and six months.

86. A method according to Claim 78, wherein the second period of time is between about one day and two months.

87. A method according to Claim 72, wherein the solution from Step (a) is used to sterilize the bioprosthetic material in a terminal sterilization step.

88. A method according to Claim 87, wherein the solution from Step (a) is used to sterilize the bioprosthetic material during Step (c).

89. A method according to Claim 88, wherein the sterilization and heat treatment of Step (c) occurs after the bioprosthetic material has been placed in a final container.

90. A method according to Claim 78, wherein the solution from Step (a) is used to sterilize the bioprosthetic material in a terminal sterilization step.

91. A method according to Claim 90, wherein the solution from Step (a) is used to sterilize the bioprosthetic material during Step (c).

92. A method according to Claim 91, wherein the sterilization and treatment of Step (c) occurs after the bioprosthetic material has been placed in a final container.